

Observational multicentric study on chronic sciatic pain: clinical data from 44 Italian centers

G.A. CHECCHIA¹, G. LETIZIA MAURO⁸, G. MORICO³, A. ORIENTE⁴,
C. LISI⁵, V. POLIMENI⁶, M. LUCIA⁷, M. RANIERI²; ON BEHALF OF
THE MANAGEMENT OF PERIPHERAL NEUROPATHIES STUDY GROUP

¹Physical Medicine and Rehabilitation Unit, Santa Corona Hospital, ASL2 Savonese, Savona, Italy

²Physical Medicine and Rehabilitation Unit, OORR Hospital, University of Foggia, Foggia, Italy

³Orthopaedic Department, "Sapienza" University of Rome, Rome, Italy

⁴Rheumatology and Rehabilitative Rheumatology Unit, "Federico II" University of Naples, Naples, Italy

⁵Rehabilitation and Functional Recovery Unit, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

⁶Physical Medicine and Rehabilitation Unit, AO "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

⁷U.O. di Anestesia e Rianimazione III, Terapia del Dolore, PO Villa Sofia, Palermo, Italy

⁸Physical Medicine and Rehabilitation Unit, AOUP "Paolo Giaccone", University of Palermo, Palermo, Italy

Abstract. – OBJECTIVE: To provide information on the clinical presentation of sciatic neuropathy and its management in a real-world setting, and to analyze the effects of a multimodal approach based on the association of physical and pharmacological therapy.

PATIENTS AND METHODS: A multicentric observational prospective study was conducted in 44 Italian tertiary centers specialized in Physical Medicine and Rehabilitation, Orthopedics, Neurology, Neurosurgery, and Rheumatology. To develop a shared management of LPB with sciatica, a dedicated clinical record was proposed to collect data about diagnosis, treatment, and outcomes. Pain, disability, and quality of life were recorded through validated questionnaires at baseline and after a two-month follow-up.

RESULTS: 394 patients (age, mean \pm SD 55.7 \pm 14.1 years, 57.1% females) with chronic LBP and sciatica were enrolled in the study. The characteristics of the selected group showed a certain variability in the clinical presentation. At baseline, patients received several different therapeutic options among physical, pharmacological and neurotrophic treatments. A subgroup of 312 patients was treated with a combination of neurotrophic agents containing alpha-lipoic acid (ALA). After a two-month follow-up, a general improvement in both perceived pain and functional disabilities was observed. A significant improvement ($p < 0.001$) in the Pain Numeric Rating Scale (NRS), Roland e Morris Disability Questionnaire (RMDQ) and Brief Pain Inventory (BPI) Italian short version was observed.

CONCLUSIONS: Sciatic neuropathy is a multifaceted condition managed by means of a wide spectrum of therapeutic options. The results of

this study suggest that a multimodal approach based on the association of ALA with physical and pharmacological therapies can be beneficial in the treatment of LBP with sciatica.

Key Words:

Mesh terms) low back pain, Sciatic neuropathy, Complementary therapies, Pain management, Alpha-lipoic acid.

Introduction

Chronic low back pain (LBP) with sciatica is defined as pain and discomfort, localized below the costal margin and above the inferior gluteal folds, with referred leg pain persisting for at least 12 weeks¹⁻⁵.

Sciatic neuropathy is among the most common peripheral neuropathies, since it is estimated to affect 5 in every 10000 Western adults⁶. Thus, it represents a social problem both in terms of patients' suffering and health costs for treating the progression of the disease. More generally speaking, LBP of at least moderate intensity and duration has an annual incidence in the adult population of 10-15% and a prevalence of 15-30%. It becomes increasingly frequent in patients older than 65 years. Therefore, a relevant number of elderly people, approximately one out of every three to four, suffers from low back pain³.

Chronic LBP with sciatica shows a broad range of clinical manifestations and consequences on patients' lives, from a preserved functionality in spite of pain to a severe disability or an interference with sleep by persistent back pain and radicular pain and paresthesia¹⁻⁵. Chronic LBP with sciatica is a quite common cause of long-term disability in middle-aged people and, due to its resistance to pharmacological and surgical interventions, requires a multimodal and multidisciplinary approach^{1,5,7}.

The economic burden of chronic LBP, in general, is relevant, spine diseases being fifth in terms of hospitalization/inpatients costs and first as a cause of absenteeism and burden of disability⁸.

The optimal management of chronic LBP with sciatica is still a matter of debate. A large panel of therapeutic options is available^{5,9-12}.

Surgery doesn't seem to be a first choice treatment for radicular neuropathy, except the cases in which it can't be avoided. A systematic review with meta-analysis of cohort studies revealed that patients with sciatica still experience pain and disability 5 years after surgery⁷.

Non-pharmacologic therapies for chronic LBP with sciatic neuropathy include acupuncture, exercise therapy, massage therapy, yoga, cognitive behavioral therapy or progressive relaxation, spinal manipulation, and intensive interdisciplinary rehabilitation. Although the level of supporting evidence for the different therapies varies from fair to good, at the moment there is no consensus about a first choice treatment⁹⁻¹¹.

Notably, recent evidence suggests that a multimodal and multidisciplinary approach involving orthopedics, physiatrists, rheumatologists, and neurologists may be the most appropriate for sciatic neuropathy. That approach also implies a detailed knowledge of pathophysiological and clinical data in order to obtain a 360-degree framework of the condition and to address the priority needs in its management.

This study focused on patients with chronic LBP with sciatica, is part of a wider project aimed at proposing an appropriate and shared management at a national level of all patients with peripheral compression neuropathy (e.g. carpal tunnel syndrome and sciatic neuropathy)¹². Thus, the Management of Peripheral Neuropathies Study Group, composed of Specialists in Physical and Rehabilitation Medicine, Orthopaedics, Neurology, Neurosurgery, Rheumatology, Anesthesiology and Pain Medicine, has designed (March-May

2012) and conducted for the following 14 months (May 2012-June 2013) this observational study aimed at providing an updated picture of chronic LBP with sciatica, including the clinical characteristics of the patients (etiology, location, severity, duration) and the management of the disease. Participating centers were outpatients care services in hospitals or in centers for outpatients care, both public or private, spread throughout Italy.

To develop a shared management of LBP with sciatica, a dedicated clinical record was proposed to collect data about diagnosis, treatment, and outcomes.

The main objectives were to determine the clinical and demographic characteristics of patients, the concomitant diseases and the response to the multimodal treatment proposed.

As regards diagnosis, we included in the clinical report the etiology, location, clinical characteristics of the disease, a complete physical examination including Lasegue's and Wassermann's maneuvers and osteotendinous reflexes, in order to propose a single shared protocol for the diagnosis of the compression neuropathy.

Previous diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy or neurotrophic agents) were also included in the clinical report.

The Study Group decided to recommend the use of neurotrophic agents, and in particular of alpha-lipoic acid (ALA), because of the increasing evidence of effectiveness in neuropathic pain and considering the good tolerability of the treatment¹²⁻²⁵.

ALA is an antioxidant that has been recently identified as a first-choice treatment for chronic neuropathic pain¹³, because of the proven effectiveness compared to placebo in the treatment of neuropathic pain¹³⁻²².

ALA exerts a protective effect on the nerve fibers, acting on the nerve inflammation and the progression of nerve damage. Furthermore, it does not interfere with other pharmacological treatments and is generally well tolerated²¹, so we decided to recommend its use as an adjuvant for the treatment of neuropathy in the patients enrolled in the study.

The study group recommended a multimodal treatment, including physical, pharmacological and neurotrophic therapies, but decided not to give a precise indication about which treatment to select within the various options. This decision was taken in order to observe the current man-

agement of sciatic pain in a real world setting.

At the same time, the study was designed to provide a feedback on the efficacy of current clinical practice and of the multimodal approach proposed, through the registration of clinical data at baseline and at the end of the follow-up. The Study Group selected the parameters to be evaluated and the questionnaires to be administered on the basis of the international literature. Among the questionnaires, the Numeric Rating Scale (NRS)^{26,27} was adopted by Pain in Europe (<http://www.paineurope.com>), the European survey about chronic pain; the Roland and Morris Disability Questionnaire (RMDQ)^{28,29} is aimed at evaluating disability; the Brief Pain Inventory-short form (BPI)^{30,31} is focused on measuring pain and its interference on activities of daily living; the Short Form-12 Health Survey (SF-12)³²⁻³⁴ is used to evaluate the quality of life.

Patients and Methods

Study Design

The observational study was carried out between May 2012 and June 2013, enrolling 394 consecutive patients with chronic LBP with sciatica followed in 44 specialized Italian centers participating in the Management of Peripheral Neuropathies Study Group (see the list of participating centers).-

The main objectives were to determine (i) the pattern of this condition; (ii) the concomitant diseases and the characteristics of patients; (iii) the response to treatments.

Patients of both genders older than 18 years with chronic (>12-week duration) LBP with sciatica were included.

A model of dedicated clinical record was developed to homogeneously collect the most relevant data about diagnosis, monitoring, and outcomes.

The study was conducted in accordance with the current guidelines of good clinical practice (GCP) regulations relating to clinical trials and the Declaration of Helsinki and was approved by the local Ethics Committee.

Informed consent was obtained from all the patients after explaining the aim of the work and the relevance of the questionnaires.

Data Collection

At baseline, the following information was collected: demographic data (age, gender, anthropometric data); lifestyle and work activity and their

relation to the condition; referral from general practitioners (GP) or specialists; comorbidities; aetiology, location, and clinical characteristics of the compression neuropathy; complete physical examination including Lasegue's and Wassermann's maneuvers and osteotendinous reflexes; previous diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy, or neurotrophic agents used for at least 10 days consecutively).

Patients were asked to state if they considered the previous treatments effective or not.

Pain Assessment

The pain was assessed by means of standardized questionnaires whose Italian translations have been previously validated: the NRS, the RMDQ, the Italian version of the BPI, and the SF-12 questionnaire.

The NRS^{26,27} is a segmented numeric horizontal bar on which patients select a whole number (from 0 "no pain" to 10 "worst possible pain") that best reflects the intensity of their pain at rest and on movement. It has become a widely used instrument for pain screening and is ubiquitous as a screener in many health care environments.

The RMDQ^{28,29} is a patient-reported measure of back pain which explore the patients' ability to perform 24 activities of daily living. Items are scored to yield a total score from 0 "no disability" to 24 "maximum disability". It is used to assess the patients' subjective rating of perceived disability and helps the clinician to address the functional limitations of the patients. Scores were categorized as follows:

- **From 0 to 9:** sub-acute or chronic LBP with mild disability (may be managed by the general practitioner);
- **From 10 to 13:** sub-acute or chronic LBP with a moderate disability;
- **> 14:** sub-acute or chronic LBP with severe disability (a multimodal and multidisciplinary management is needed).

The BPI³⁰ is a self-administered assessment tool which measures pain interference. It consists of 9 items measuring interference, experience of pain on the current day, and localization of pain occurrence. Scores are assigned on a scale from 0 "does not interfere" to 10 "completely interferes". Its short form³¹ is used for clinical trials and translated in foreign languages, as in the case of the short Italian version named BQVD, Breve Questionario per la Valutazione del Dolore).

Scores were categorized as follows:

- Factor 1 – Pain intensity (range 0-50);
- Factor 2 – Affective interference (range 0-30);
- Factor 3 – Activity interference (range 0-30).

The SF-12³²⁻³⁴ is a generic health status measure including 12 items which yield a profile of functional health and well-being. It is recommended for self-administration, brevity, simplicity, validity and reliability.

Statistical Analysis

Quantitative variables were reported as mean \pm standard deviation (SD) and range, qualitative variables as absolute and relative frequencies. Data were summarized in tables and figures as appropriate.

The data collected were analyzed by standard descriptive statistics.

The intragroup differences in NRS, RMDQ, BPI (baseline vs. end of follow-up) were assessed by means of paired *t*-test. Differences have been considered significant where $p < 0.05$.

As regards the SF-12, we only reported the variation of the answers to each item, so as to point out which ones were more influenced by the treatments.

No direct comparison of the treatments was performed.

No missing data have been replaced and no replacement policy has been implemented; as a matter of fact, the analysis fully reflects the observed values.

The statistical analysis has been performed using the software SPSS Statistical Package, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Baseline characteristics of the 394 patients (age, mean \pm SD 55.7 ± 14.1 years, 57.1% females) with chronic LBP with sciatica enrolled in the study are reported in Table I. Among all patients, 12.4% were menopausal and 2% pregnant women.

For the majority of patients (63.5%) time since the initial diagnosis ranged from 3 to 12 months, while for the others initial diagnosis was made more than one year before enrolment. The most common comorbidities were osteoarthritis (28.2%), diabetes (19.3%), osteoporosis (17%), thyroid disorders (10.9%) and rheumatoid arthritis (3.6%).

Physical Examination

Following physical examination, patients were classified as having: sciatica (82.7%, $n = 326$), low back pain (9.4%, $n = 37$), cruralgia (3.6%, $n = 14$). The diagnosis after the physical examination was missing in 17 (4.3%) patients.

As regards semiotic maneuvers a positivity in Lasègue's test was observed in 68.8% of patients, and a positivity in Wassermann's test in 30.2% of patients. Osteotendinous reflexes were normal in 47.2%, reduced in 36.3%, absent in 3.5% of patients. Muscle wasting was observed in 26.7% of patients.

49.7% of patients reported diurnal paresthesia and 45.9% reported nocturnal paresthesia.

Instrumental Diagnostic Procedures

Considering diagnostic imaging, 52.3% ($n = 206$) of patients underwent conventional X-ray,

Table I. Demographic and clinical characteristics of patients at baseline.

	All patients (N = 394)
Gender	no. (%)
- Female	225 (57.1%)
- Male	169 (42.9%)
Age (years)	55.7 \pm 14.1
mean \pm SD (range)	(25-87)
Body weight (kg)	73.4 \pm 12.9
mean \pm SD (range)	(47-120)
Height (cm)	168.7 \pm 8.5
mean \pm SD (range)	(140-197)
BMI (kg/m ²)	26.1 \pm 4.2
mean \pm SD (range)	(17.9-43.8)
BMI categories (reference values)	no. (%)
- Underweight (< 18.5 kg/m ²)	2 (0.5%)
- Normal weight (18.5-24.9 kg/m ²)	165 (41.9%)
- Overweight (25-29.9 kg/m ²)	143 (36.3%)
- Obesity (≥ 30 kg/m ²)	62 (15.7%)
- ND	22 (5.6%)
Smoking habit	no. (%)
1. No	226 (57.3%)
2. Yes	122 (31.0%)
- ND	46 (11.7%)
Work activity no. (%)	no. (%)
1. Blue collar	59 (15.0%)
2. White collar	103 (26.1%)
3. Homemaker	82 (20.8%)
4. Retiree	79 (20.1%)
5. Others	63 (16.0%)
- ND	8 (2.0%)
Work-related chronic back pain	no. (%)
1. No	169 (42.9%)
2. Yes	80 (20.3%)
3. Uncertain	106 (26.9%)
- ND	39 (9.9%)

ND: Not determined.

Table II. Baseline treatments before enrolment.

	Patients treated (no.)	Clinical response		
		No	Yes	ND
Physical therapy no. (%)				
Corset	89	25 (28.1%)	51 (57.3%)	13 (14.6%)
Laser/Carbon dioxide laser	66	34 (51.5%)	19 (28.8%)	13 (19.7%)
Electroanalgesia	36	21 (58.3%)	6 (16.7%)	9 (25.0%)
Ultrasound	51	27 (52.9%)	14 (27.5%)	10 (19.6%)
TENS	85	44 (51.8%)	27 (31.8%)	14 (16.5%)
Diadynamic	42	23 (54.8%)	7 (16.7%)	12 (28.6%)
Others	24	13 (54.2%)	8 (33.3%)	3 (12.5%)
Pharmacological therapy no. (%)				
NSAIDs	226	86 (38.1%)	97 (42.9%)	43 (19.0%)
Corticosteroids (oral)	88	19 (21.6%)	52 (59.1%)	17 (19.3%)
Corticosteroids (infiltration)	43	7 (16.3%)	19 (44.2%)	17 (39.5%)
Paracetamol	94	49 (52.1%)	37 (39.4%)	8 (8.5%)
Opioids	42	6 (14.3%)	25 (59.5%)	11 (26.2%)
Others	29	14 (48.3%)	11 (37.9%)	4 (13.8%)
Neurotrophic therapy no. (%)				
ALA	37	6 (16.2%)	24 (64.9%)	7 (18.9%)
Carnitine	46	16 (34.8%)	9 (19.6%)	21 (45.7%)
B complex vitamins	61	21 (34.4%)	9 (14.8%)	31 (50.8%)
Others	9	4 (44.4%)	4 (44.4%)	1 (11.1%)

57.4% (n = 226) nuclear magnetic resonance (NMR), and 17.5% (n = 69) computed tomography (CT). Electromyography was performed in 10.7% (n = 42) of patients.

Final Diagnosis

All in all, the most prevalent conditions were herniated disc in 53.8% (n = 212) of patients and disc space narrowing in 11.9% (n = 47).

Baseline Treatments Before Enrolment

Previous treatments before enrolment had been prescribed by the GPs in 62.9% of patients, by a specialist in 32.5%. The response to previous treatments, classified in three main categories (physical therapy, pharmacological therapy, and neurotrophic therapy), is reported in Table II. Physical therapy interventions were associated to low response rates (in general less than a third of patients) with the exclusion of corset (57.3% of responders), TENS (31.8%), laser/carbon dioxide laser (28.8%), and ultrasound (27.5%). Response rates to pharmacological therapy ranged between 39.4% and 59.5% with the different options. Among neurotrophic medications, only ALA obtained satisfactory response rates (64.9%).

Prescribed Treatments

The prescribed treatments at baseline, classified in the same three main categories, are reported in Table III.

A wide variability in the interventions was apparent. The most prescribed physical treatments were TENS (28.9%) and corsets (26.1%).

Table III. Prescribed treatments.

	All patients No. (%)
Physical therapy	
Corset	103 (26.1%)
Laser/Carbon dioxide laser	60 (15.2%)
Electroanalgesia	34 (8.6%)
Ultrasound	47 (11.9%)
TENS	114 (28.9%)
Diadynamic	28 (7.1%)
Others	104 (26.4%)
Pharmacological therapy	
NSAIDs	135 (34.3%)
Corticosteroids (oral)	59 (15.0%)
Corticosteroids (infiltration)	33 (8.4%)
Paracetamol	101 (25.6%)
Opioids	75 (19.0%)
Others	40 (10.2%)
Neurotrophic agents	
ALAnerv ON	226 (57.4%)
ALA600 SOD	86 (21.8%)
Carnitine	27 (6.9%)
B complex vitamins	14 (3.6%)
Others	10 (2.5%)

As regards pharmacological therapy, NSAIDs and paracetamol (34.3% and 25.6%, respectively) were more frequently used than corticosteroids (oral 15% and infiltration 8.4%). A considerable amount of cases (19%) required opioids.

Among neurotrophic agents, the most prescribed were ALAnerv ON® (ALA 300 mg, gamma-linolenic acid, GLA, 180 mg, honokiol 27 mg, selenium 25 µg, vitamin B1 1.05 mg, vitamin B2 1.2 mg, vitamin B5 4.5 mg, vitamin B6 1.4 mg, vitamin E 7.5 mg, and selenium 25 µg; Alfa Wassermann, Bologna, Italy) and ALA600 SOD® (ALA 600 mg, superoxide dismutase, SOD, 140 IU/day, vitamin E 7.5 mg, and selenium 25 µg; Alfa Wassermann, Bologna, Italy). The associations have been prescribed to 57.4% and 21.8% of patients, respectively. The use of carnitine or B complex vitamins was relatively limited, accounting for approximately 10%.

At the final evaluation after a two-month follow-up, the compliance to treatments and the need for dose changing were recorded.

Physical therapy was completed as planned in 65.2% of patients.

Considering pharmacological therapy, daily administration schedule was unchanged in 72.1% of patients and withdrawn in 1.5%; while a dose increase was needed in 9.4% of patients, and a dose reduction in 4.1%.

Considering neurotrophic therapy, daily administration schedule was unchanged in 78.7% of patients and withdrawn in 2.5%; while a dose increase was needed in 4.1% of patients, and a dose reduction in 3.8%.

An analysis of patients' characteristics according to the prescribed treatments is reported in Table IV. The analysis focuses on the association of physical, pharmacological and neurotrophic therapies and their prescription according to age, gender and intensity of pain (mild, moderate, severe according to the NRS scale). We observed a good adherence to the recommendation of the Study Group to adopt a multimodal strategy, with a greater prescription of all the three categories of treatments (neurotrophic, pharmacological and physical) in the patients with the higher levels of pain.

Pain and Disability Scores

At the end of the study, a general improvement in both perceived pain and functional disabilities was observed.

Specifically, the NRS (cases assessed, baseline vs. end of follow-up 360 vs. 341) significantly improved in both pain at rest (baseline vs. end of follow-up, mean \pm SD 6.6 ± 2.2 vs. 2.1 ± 1.8 , $p < 0.001$) and pain on movement (7.6 ± 1.9 vs. 2.6 ± 1.8 , $p < 0.001$).

Table IV. Prescribed treatments according to patients' characteristics and pain intensity.

	NO NT (Phys T or Phar T or both)	Prescribed therapy				Total
		NT	NT + Phys T	NT + Phar T	NT + Phys T + Phar T	
Patients No.	33	25	44	87	205	394
Age						
< 65 years	24 (75.0%)	15 (60.0%)	29 (67.4%)	63 (73.3%)	149 (73.0%)	280 (71.8%)
≥ 65 years	8 (25.0%)	10 (40.0%)	14 (32.6%)	23 (26.7%)	55 (27.0%)	110 (28.2%)
Gender						
- Female	17 (53.1%)	18 (72%)	23 (54.8%)	45 (51.7%)	119 (58.6%)	222 (57.1%)
- Male	15 (46.9%)	7 (28.0%)	19 (45.2%)	42 (48.3%)	84 (41.4%)	167 (42.9%)
NRS at rest						
Mild (1-3)	2 (7.7%)	4 (16.6%)	5 (12.2%)	8 (10.1%)	7 (3.7%)	26 (7.3%)
Moderate (4-6)	9 (34.6%)	10 (41.7%)	17 (41.5%)	18 (22.8%)	67 (35.7%)	121 (33.8%)
Severe (7-10)	15 (57.7%)	10 (41.7%)	19 (46.3%)	53 (67.1%)	114 (60.6%)	211 (58.9%)
NRS on movement						
Mild (1-3)	0 (0%)	1 (4.2%)	1 (2.4%)	1 (1.2%)	7 (3.7%)	10 (2.8%)
Moderate (4-6)	1 (4.0%)	10 (41.6%)	16 (39.1%)	16 (19.8%)	35 (18.5%)	78 (21.6%)
Severe (7-10)	24 (96%)	13 (54.2%)	24 (58.5%)	64 (79.0%)	147 (77.8%)	272 (75.6%)

NT: Neurotrophic Therapy; Phys T: Physical Therapy; Phar T: Pharmacological Therapy.

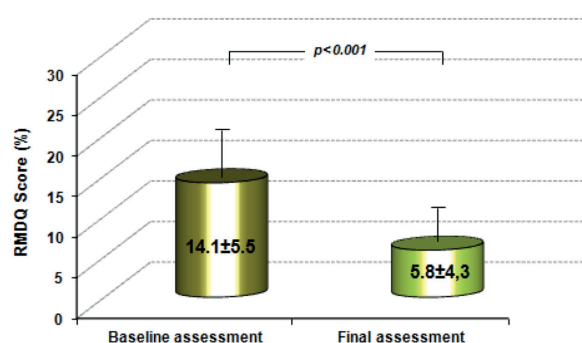


Figure 1. Roland and Morris Disability Questionnaire (RMDQ) at baseline and at the end of treatment.

The RMDQ mean proportion of positive responses (cases assessed 203 vs. 192) passed from $14.1 \pm 5.5\%$ to $5.8 \pm 4.3\%$ ($p < 0.001$) (Figure 1). For all the items a trend towards a reduction (ranging from -3% to -59%) was observed.

An improvement in all three factors of BPI short Italian version was recorded (factor 1, pain intensity 284 ± 93 vs. 111 ± 84 ; factor 2, affective interference 150 ± 76 vs. 47 ± 57 ; factor 3, activity interference 186 ± 65 vs. 74 ± 59 , $p < 0.001$ for all). Pain relief from any treatment in the last 24 hours was reported more frequently at the end of the study ($39.6 \pm 20.6\%$ vs. $60.4 \pm 29.2\%$, $p < 0.001$).

An improvement in all the SF-12 items was observed (Table V).

Discussion

This observational study with descriptive purposes provides a “real life” representation of chronic LBP with sciatica in Italy, in terms of patients’ characteristics and therapeutic interventions.

The group of patients selected is likely representative of the whole population suffering from this condition: young-elderly, the onset of signs and symptoms generally occurring in the last 12 months, a broad range of causes, clinical presentation and radiologic features.

However, the presence of pain and disability is a quite common aspect, confirming the high burden on health and on quality of life of chronic LBP with sciatica.

Similarly, a wide variability in the management of the disease is apparent. This is consistent with the fact that guidelines do not express homogeneous and straightforward recommendations⁹⁻¹¹.

Notably, according to the Italian Diagnostic, Clinical and Therapeutic pathway for patients with LBP³⁵, the first level approach should include, in both acute and chronic conditions, counseling, modification of daily life, and active lifestyle, followed by conventional palliative medical treatment and rehabilitation. This latter aimed at functional recovery by means of several different interventions (exercises, cognitive-behavioral therapy, back school and multidisciplinary treatments).

Unfortunately treatment guidelines usually refer to LBP with or without sciatica as a unique pathology. So, as the targets are both LBP and neuropathic sciatic pain, a multimodal strategy targeting both kinds of pain should be followed.

At the moment considering the individual patient’s characteristics, including not only the symptoms but also the level of disability, is advised. Therefore, there is consensus about a multimodal and multidisciplinary approach, focused on the pathophysiology of the disease, and more specifically acting on two main directories: pain and disability.

As far as the pharmacological treatments are concerned, when choosing the pharmacological therapy, typically anti-inflammatory and analgesic medications, the average age of patients with chronic LBP and the even increasing prevalence in the older population have to be taken into account to prevent a higher occurrence of side effects and reach an acceptable harm to benefit ratio. To this aim, pathogenetic therapies represent a promising option and, accordingly, their prescription is recommended in neuropathic pain^{13,14}.

A recent Post-hoc analysis of the NATHAN I trial, in which patients with diabetic neuropathy were treated with ALA 600 mg/day by oral route for 4 years, highlighted the significant effectiveness of ALA in particular in older people (>65 years), with a significant reduction in the Neuropathy Impairment Score (NIS) vs. placebo²¹.

Among neuropathic mechanisms of sciatica pain, oxidative stress which develops after the peripheral neuropathic lesion is acknowledged as a relevant factor responsible for neuropathic pain, leading to the activation of an inflammatory pathway involving the whole peripheral nerve up to the spinal dorsal horn, and, subsequently, of microglia³⁶⁻³⁹. This process may result in spine sensitization and in chronic neuropathic pain^{14,38}.

Recently, ALA and superoxide dismutase (SOD), another antioxidant agent endowed with

Table V. SF-12 Health Survey Questionnaire at baseline and at the end of treatment.

	Baseline	Final
1. In general, would you say your health is		
Excellent	0.6%	1.3%
Very good	7%	23.9%
Good	43.6%	50.3%
Fair	31.4%	21.4%
Poor	17.4%	3.1%
<i>Does your health now limit you in these activities? If so, how much?</i>		
2. Moderate activities		
Yes, limited a lot	61.6%	9.9%
Yes, limited a little	34.3%	62.3%
No, not limited at all	4.1%	27.8%
3. Climbing several flights of stairs		
Yes, limited a lot	48.3%	5.6%
Yes, limited a little	42.4%	54.9%
No, not limited at all	9.3%	39.5%
<i>During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?</i>		
4. Accomplished less than you would like		
Yes	84.8%	38.3%
No	15.2%	61.7%
5. Were limited in the kind of work or other activities		
Yes	91.2%	58%
No	8.8%	42%
<i>During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?</i>		
6. Accomplished less than you would like		
Yes	78.4%	29.4%
No	21.6%	70.6%
7. Did work or activities less carefully than usual		
Yes	57.3%	13.9%
No	42.7%	86.1%
8. During the past 4 weeks, how much did pain interfere with your normal work (including both housework and work outside the home)?		
Not at all	1.2%	4.4%
A little bit	2.3%	38.1%
Moderately	26.9%	45%
Quite a bit	48.5%	10%
Extremely	21.1%	2.5%
<i>How much of the time during the past 4 weeks</i>		
9. Have you felt calm and peaceful?		
All of the time	1.2%	12.7%
Most of the time	15.3%	36.1%
A good bit of the time	7.1%	20.8%
Some of the time	45.3%	22.2%
A little of the time	22.9%	6.3%
None of the time	8.2%	1.9%
10. Did you have a lot of energy?		
All of the time	1.8%	7.1%
Most of the time	5.9%	22.4%
A good bit of the time	5.9%	23.1%
Some of the time	29.3%	35.2%
A little of the time	40%	9.6%
None of the time	17.1%	2.6%

Table continued

Table V (Continued). SF-12 Health Survey Questionnaire at baseline and at the end of treatment.

	Baseline	Final
11. Have you felt downhearted and depressed?		
All of the time	9.3%	2.5%
Most of the time	14%	3.8%
A good bit of the time	20.5%	5.7%
Some of the time	32.2%	28.9%
A little of the time	19.3%	44.7%
None of the time	4.7%	14.4%
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?		
All of the time	7.6%	2.5%
Most of the time	19.9%	2.5%
Some of the time	33.3%	7.5%
A little of the time	31%	44.4%
None of the time	8.2%	43.1%

anti-inflammatory properties^{40,41}, have been proven effective in the management of diabetic neuropathy⁴², low back pain⁴³, and chronic neck pain⁴⁴.

Therefore, antioxidant agents like ALA and SOD may be a useful choice in the multimodal treatment strategy for chronic LBP patients, since they can contribute to pain control due to their prevalently anti-inflammatory action⁴²⁻⁴⁴.

The benefit of ALA in association with neurotrophic agents has been demonstrated in patients with chronic conditions characterized by an impairment in the nerve fiber function. Clinical trials on patients with radiculopathies and carpal tunnel syndrome show that the combination of ALA and GLA, a polyunsaturated n-3 (omega-3) fatty acid, exerts a synergistic positive effect on symptoms and peripheral nerve fiber conduction^{19,20,24}. Neurotrophic agents such as GLA, honokiol and vitamin B complex have been used in association with ALA to improve sensory-motor function^{12,23-25}.

Antioxidant and neurotrophic agents may contribute to pain control, thus allowing to reduce analgesic medications and, as a consequence, to improve the safety profile of the therapeutic strategy adopted.

On the other hand, the effectiveness of physical therapies is controversial because of the lack of high quality clinical trials^{9-12,45,46}. Transcutaneous electrical nerve stimulation (TENS) is based on the delivering of electrical stimulation to the underlying nerves via electrodes placed over the intact skin surface near the source of maximal pain.

Four high-quality randomised controlled trials (585 patients) comparing TENS with placebo for chronic low-back pain have been published. Due

to conflicting evidence, it is unclear if TENS is beneficial in reducing back pain intensity⁴⁵.

It has to be highlighted that any intervention has to be considered in the framework of a multidisciplinary approach in order to address the various pathogenetic mechanisms with an appropriate multimodal treatment.

On the base of these considerations, our Study Group decided to recommend a multimodal approach including pharmacological, physical and neurotrophic treatments, with particular consideration to ALA, that has the higher degree of evidence among neurotrophic agents in neuropathic pain. We decided not to recommend a particular kind of pharmacological or physical treatment. The reason for this is that patients enrolled suffered from different levels of pain (mild, moderate or severe) and could be suffering from various comorbidities, thus a unique drug could not be recommended for all the patients. Furthermore, as regards physical therapies there is not a clear indication from literature and the participating centers could not have all the instruments for the various physical therapies available, so we decided to let the centers have freedom of choice in the pharmacological and physical treatments on the basis of patients' characteristics.

In this investigation, we observed a clinically significant improvement in symptoms, disability and quality of life.

Key results of the study are in our opinion the general and considerable improvement in both perceived pain (NRS and BPI) and functional disability (RMDQ), that can be considered a remarkable result, considering that the most effective drugs used alone for neuropathic pain have a NRS pain reduction vs. placebo ranging

from -1.30 for gabapentin to -1.06 for duloxetine¹⁷. Furthermore, we observed a good adherence to the recommendation of the Study Group to adopt a multimodal strategy, with a greater prescription of all the three categories of treatments (neurotrophic, pharmacological and physical) in the patients with the higher levels of pain.

This report has several limitations, as it is an observational study which comprises a wide variety of treatments and can't demonstrate the effectiveness of a particular treatment or of an association of treatments. It can only suggest that the association of ALA with pharmacological and physical therapies produce a clinically significant improvement in pain, functional disability and quality of life in patients suffering from LBP with sciatica.

Another limitation is that, although the Study group recommended to include in the study only patients suffering from LBP with sciatica, a little percentage of the patients enrolled didn't have a clear diagnosis of sciatic neuropathy. Despite this data, we considered all the patients included by the centers for the analysis, in the certainty that they all were endowed with a neuropathic component in LBP.

Conclusions

This study describes a likely representative population of patients suffering from chronic LBP with sciatica whose conditions were carefully assessed by means of standardized and validated questionnaires and followed prospectively for 2 months. Since a multimodal and multidisciplinary approach was adopted, a broad range of therapeutic options were used, which resulted in a general improvement in both perceived pain and functional disabilities. These results suggest that a multimodal approach can be beneficial in the treatment of LBP with sciatica.

Notes

This study was presented at the 42nd Meeting of the Italian Society of Physical and Rehabilitation Medicine (Società Italiana di Medicina Fisica e Riabilitativa, SIMFER), Turin 28th September-1st October 2014.

We acknowledge the Participants and Contributors to the Study

APRILE ANTONELLA, Centro di Riabilitazione dei Padri Trinitari, Gagliano Del Capo (LE), Italy
BALDASSARRE VINCENZO, UOSS Riabilitazione delle patologie degenerative del rachide, Ospedale Cardarelli, Naples, Italy

BARBIERI MAURIZIO, Medicina Fisica e Riabilitazione, Ospedale Civile Ciriè, ASL Torino 4, Turin, Italy
BRAINA PIETRO, Fiduciario Medico FIGC – Medicina Fisica e Riabilitativa, Azienda Ospedaliera Brotzu, Cagliari, Italy
BRISCHITTI GAETANO, Ambulatorio Ortopedia del Presidio Territoriale di Assistenza ASP, Siracusa, Italy
CALORIO LIVIA, Recupero e Rieducazione Funzionale, Poliambulatorio Kinesiterapico Tesoriera s.r.l., Turin, Italy
CAMPAGNOLI MARCELLO, SCU Medicina Fisica e Riabilitazione, ASO Città della Salute e della Scienza, Turin, Italy
CAPPELLETTI CRISTINA, SC Ortopedia e Traumatologia, Ospedale Civile Ciriè, ASL Torino 4 Turin, Italy
CASILLO GIUSEPPE, Centro Agroaversano, ASL Caserta 2, Aversa (CE), Italy
CERIMELE DANIELE, UO Ortopedia e Traumatologia, Presidio Ospedaliero San Francesco Caracciolo, Agnone (IS), Italy
CORONA MASSIMILIANO, Reparto Ortopedia e Traumatologia, Ospedale San Timoteo, Termoli (CB), Italy
CORTESE ANNALISA, Specialista in Medicina Fisica e Riabilitazione, F.P.J. Don Gnocchi, Turin, Italy
DE ROBERTO SALVATORE, FRANZE' FRANCO, SOC Recupero e Rieducazione Funzionale Ospedale San Lazzaro di Alba e S. Spirito di Brà, ASL CN 2, Cuneo, Italy
DI BONITO MARIO, Ortopedia e Traumatologia, ASL Napoli 2, Naples, Italy
DI GREGORIO LUCIA, Ambulatorio Reumatologia dell'Istituto Ortopedico Villa Salus, Augusta (SR), Italy
DI MEO GRAZIELLA, UOG Lungodegenza, Presidio Ospedaliero Ospedale G. Vietri, Larino (CB), Italy
FANTON ERIKA, SC Recupero e Rieducazione Funzionale, Presidio Ospedaliero Sant'Andrea, Vercelli, Italy
FRANCESE FABIO, Responsabile Sanitario Novara Calcio, Italy
FRESU SILVIA, Specialista in medicina fisica e riabilitativa, ASL 7 Carbonia (CI), Italy
GIRONE MARIAGAIA, CASIRAGHI ANNA, IRCCS S. Maria Nascente, Fondazione Don Gnocchi, Milan, Italy
IMAZIO PAOLA, SS Recupero e Rieducazione Funzionale di Chieri, ASL Torino 5, Chieri (TO)
LETIZIA MAURO GIULIA, SCATURRO DALILA, CHIAPPONE MARYLENA, ASARO CHIARA, UOC di Riabilitazione AOUN "Paolo Giaccone", Palermo, Italy
LISI CLAUDIO, DI NATALI GIUSEPPE, SC di Riabilitazione e Recupero Funzionale, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
LOIERO MARIO, UO di Neurologia, Istituto Gaetano Pini, Milan, Italy
LUCIA MARIA, BONTÀ TANIA, CUFFARO LORENA, U.O. di Anestesia e Rianimazione III, Terapia del Dolore, PO Villa Sofia, Palermo, Italy
MARINI ANDREA, Servizio Recupero e Rieducazione Funzionale, Ospedale Oncologico A. Businco, Azienda Ospedaliera Brotzu, Cagliari, Italy
MELIS GIANCARLO, Ortopedia e Traumatologia, Ospedale A. Segni, Ozieri (SS), Italy
MISAGGI BERNARDO, LA MAIDA GIOVANNI ANDREA, PERONI DONATA RITA, FERRARO MARCELLO, RE VALENTINA, ZOTTARELLI LEONARDO, Centro Patologie Della Colonna Vertebrale, Istituto Gaetano Pini, Milan, Italy
MORICO GIANFRANCO, Clinica Ortopedica, Università "LA SAPIENZA" di Roma (RM)

ORFEI MATTEO, Centro di Riabilitazione intensiva/estensiva, Istituto Prosperius Tiberino SPA, Umbertide (PG), Italy
 ORIENTE ALFONSO, AF Reumatologia e Riabilitazione Reumatologica, Università di Napoli Federico II, Naples, Italy
 PARDI ALESSANDRO, UOC Ortopedia, Ospedale San Luca, ASL 2, Lucca, Italy
 POLIMENI VINCENZO, UO di Fisiatria, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy
 POSTERARO GIUSEPPE, Ambulatorio di Fisiatria, ASP Paola (CS), Italy
 QUERCIO MARCO, Direttore FF SC Medicina Riabilitativa, Ospedale SS Trinità, ASL CN1, Fossano (CN), Italy
 RANDO GIANCARLO, SOCRRF Ospedale San Lazzaro di Alba (CN), ASL CN 2, Cuneo, Italy
 RUOSI CARLO, Dipartimento di Sanità Pubblica, Sezione di Ortopedia, Università degli Studi di Napoli Federico II, Naples, Italy
 RUSSO FLAVIO, Ambulatorio di Fisiatria del Distretto Sanitario di Isernia, Isernia, Italy
 SCHEMBRI BARBARA, Centro LING di Rieducazione Neuromotoria e Fisioterapia, Palermo, Italy
 TORRESANI DANIELA, Dipartimento Riabilitativo, Ospedale Fracastoro, San Bonifacio USSL 20 Verona, Italy
 ZOLELIO PIERLUIGI, Servizio Recupero e Rieducazione Funzionale, Ospedale Oncologico A. Businco, ASL 8, Cagliari, Italy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- BRATTON RL. Assessment and management of acute low back pain. *Am Fam Physician* 1999; 60: 2299-2308.
- AIRAKSINEN O, BROX JI, CEDRASCHI C, HILDEBRANDT J, KLABER-MOFFETT J, KOVACS F, MANNION AF, REIS S, STAL JB, URSIN H, ZANOLI G. COST B13 Working group on guidelines for chronic low back pain. European guidelines for the management of non specific low back pain. *Eur Spine J* 2006; 15: S192-300.
- ANDERSSON GB. Epidemiological features of chronic low back pain. *Lancet* 1999; 354: 581-585.
- KARAMAN S, KARAMAN T, DOGRU S, ONDER Y, CITIL R, BULUT YE, TAPAR H, SAHIN A, ARICI S, KAYA Z, SUREN M. Prevalence of sleep disturbance in chronic pain. *Eur Rev Med Pharmacol Sci* 2014; 18: 2475-2481.
- ROPPER AH, ZAFONTE RD. Sciatica. *N Engl J Med* 2015; 372: 1240-1248.
- CHERKIN DC, DEYO RA, LOESER JD, BUSH T, WADDELL G. An international comparison of back surgery rates. *Spine* 1994; 19: 1201-1206.
- MACHADO GC, WITZLEB AJ, FRITSCH C, MAHER CG, FERREIRA PH, FERREIRA ML. Patients with sciatica still experience pain and disability 5 years after surgery: A systematic review with meta-analysis of cohort studies. *Eur J Pain* 2016; 20: 1700-1709.
- PEUL WC, VAN HOUWELINGEN HC, VAN DENHOUT WB, BRAND R, EEKHOF JAH, TANS JTJ, THOMEER RTWM, KOS BW FOR THE LEIDEN-THE HAGUE SPINE INTERVENTION PROGNOSTIC STUDY GROUP. Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med* 2007; 356: 2245-2256.
- CHOU R, QASEEM A, SNOW V, CASEY D, CROSS JT JR, SHEKELLE P, OWENS DK; CLINICAL EFFICACY ASSESSMENT SUBCOMMITTEE OF THE AMERICAN COLLEGE OF PHYSICIANS; AMERICAN COLLEGE OF PHYSICIANS; AMERICAN PAIN SOCIETY LOW BACK PAIN GUIDELINES PANEL. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147: 478-491.
- ITALIAN SOCIETY OF ORTHOPAEDICS AND TRAUMATOLOGY (SIOT) GUIDELINES. Mal di schiena. Banca dati comparativa tra Linee Guida e analisi critica delle raccomandazioni. *GIOT* 2011; 37: 113-130.
- NATIONAL INSTITUTE OF HEALTH AND CLINICAL EXCELLENCE (NICE). Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guidelines CG173 2013. Available at: <http://publications.nice.org.uk/neuropathic-pain-pharmacological-management-cg173>.
- LUCHETTI R, TOGNON S, CACCIAVILLANI M, RONCO S, BUZZELLI N, LANNI G. Observational multicentric survey on carpal tunnel syndrome: demographic and clinical data from 34 Italian centers. *Eur Rev Med Pharmacol Sci* 2017; 21: 460-469.
- WATSON JC, DYCK PJB. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. *Mayo Clin Proc* 2015; 90: 940-951.
- LEE FH, RAJA SN. Complementary and alternative medicine in chronic pain. *Pain* 2011; 152: 28-30.
- COSTANTINO M, GUARALDI C, COSTANTINO D, DE GRAZIA S, UNFER V. Peripheral neuropathy in obstetrics: efficacy and safety of α-lipoic acid supplementation. *Eur Rev Med Pharmacol Sci* 2014; 18: 2475-2481.
- KAPOOR S. Clinical applications of alpha-lipoic acid in the management of neurological disorders besides carpal tunnel syndrome. *Eur Rev Med Pharmacol Sci* 2009; 13: 401-402.
- SNEDECOR SJ, SUDHARSHAN L, CAPPELLERI JC, SADOSKY A, MEHTA S, BOTTEMAN M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. *Pain Pract* 2014; 14: 167-184.
- MIJNHOUT GS, KOLLEN BJ, ALKHALAF A, KLEEFSTRA N, BILO HJ. Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol* 2012; 2012: 456-279.
- RANIERI M, SCIUSCIO M, MUSCI L. Efficacia e sicurezza della supplementazione con acido alfa-lipoico (ALA) e acido gamma-linolenico (GLA) nel trattamento della rachialgia: studio osservazionale preliminare. *Eur Med Phys* 2008; 44: 1-4.

- 20) RANIERI M, SCIUSCIO M, CORTESE AM, SANTAMATO A, DI TEO L, IANIERI G, BELLOMO RG, STASI M, MEGNA M. The use of alpha-lipoic acid (ALA), gamma linolenic acid (GLA) and rehabilitation in the treatment of back pain: effect on health-related quality of life. *Int J Immunopathol Pharmacol* 2009; 22(S3): 45-50.
- 21) ZIEGLER D, LOW PA, FREEMAN R, TRITSCHLER H, VINIK AI. Predictors of improvement and progression of diabetic polyneuropathy following treatment with α -lipoic acid for 4 years in the NATHAN 1 trial. *J Diabetes Complications* 2016; 30: 350-356.
- 22) MEMEO A, LOIERO M. Thiocctic acid and acetyl-L-Carnitine in the treatment of sciatic pain caused by herniated disc. *Clin Drug Invest* 2008; 28: 495-500.
- 23) FAN YY, CHAPKIN RS. Importance of dietary gamma-linolenic acid in human health and nutrition. *J Nutr* 1998; 128: 1411-1414.
- 24) DI GERONIMO G, CACCESE AF, CARUSO L, SOLDATI A, PASSARETTI U. Treatment of carpal tunnel syndrome with alpha-lipoic acid. *Eur Rev Med Pharmacol Sci* 2009; 13: 133-139.
- 25) HOI PC, HO YP, BAUM L, CHOW AH. Neuroprotective effect of honokiol and magnolol, compounds from *Magnolia officinalis*, on beta-amyloid-induced toxicity in PC12 cells. *Phytother Res* 2010; 24: 1538-1542.
- 26) HARTRICK CT, KOVAN JP, SHAPIRO S. The numeric rating scale for clinical pain measurement: a ratio measure? *Pain Pract* 2003; 3: 310-316.
- 27) FARRAR JT, YOUNG JP JR, LAMOREAUX L, WERTH JL, POOLE RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94: 149-158.
- 28) ROLAND M, MORRIS RW. A study of the natural history of back pain. Part 1: Development of a reliable and sensitive measure of disability in low back pain. *Spine* 1983; 8: 141-144.
- 29) ROLAND M, FAIRBANK J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine* 2000; 25: 3115-3124.
- 30) ATKINSON TM, ROSENFELD BD, SIT L, MENDOZA TR, FRUSCIONE M, LAVENE D, SHAW M, LI Y, HAY J, CLEELAND CS, SCHER HI, BREITBART WS, BASCH E. Using confirmatory factor analysis to evaluate construct validity of the Brief Pain Inventory (BPI). *J Pain Symptom Manage* 2011; 41: 558-565.
- 31) CLEELAND CS, RYAN KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; 23: 129-138.
- 32) WARE JE JR, SHERBOURNE CD. The MOS 36 Item Short Form Health Survey (SF 36). Conceptual framework and item selection. *Med Care* 1992; 30: 473-83.
- 33) WARE JE, KOSINSKI M, KELLER SD. A 12-item short form health survey. Construction of scales and preliminary tests of reliability and validity. *Med Care* 1995; 34: 220-33.
- 34) APOLONE G, MOSCONI P, QUATTROCIOCCHI L, GIANICOLO EAL, GROTH N, WARE JJE. Questionario sullo stato di salute SF-12 versione italiana, 2005. Available at: <http://crc.marionegri.it/qdv/downloads/SF12%20Manuale.pdf>.
- 35) GIOVANNONI S, MINOZZI S, NEGRINI S. Percorsi diagnostico terapeutici per l'assistenza ai pazienti con mal di schiena. Pacini publisher, 2006 Available at: <http://www.gss.it/gss/lombalgia/PDTLombalgia.pdf>
- 36) VINCENT AM, EDWARDS JL, SADIDI M, FELDMAN EL. The antioxidant response as a drug target in diabetic neuropathy. *Curr Drug Targets* 2008; 9: 94-100.
- 37) BERGER JV, KNAEPEN L, JANSSEN SP, JAKEN RJ, MARCUS MA, JOOSTEN EA, DEUMENS R. Cellular and molecular insights into neuropathy-induced pain hypersensitivity for mechanism-based treatment approach. *Brain Res Rev* 2011; 67: 282-310.
- 38) VALLEJO R, TILLEY DM, VOGEL L, BENYAMIN R. The role of glia and the immune system in the development and maintenance of neuropathic pain. *Pain Pract* 2010; 10: 167-184.
- 39) KIM HY, CHUNG JM, CHUNG K. Increased production of mitochondrial superoxide in the spinal cord induces pain behaviours in mice: the effect of mitochondrial electron transport complex inhibitors. *Neurosci Lett* 2008; 447: 87-91.
- 40) NAKAJIMA S, OHSAWA I, NAGATA K, OHTA S, OHNO M, IJICHI T, MIKAMI T. Oral supplementation with melon superoxide dismutase extract promotes antioxidant defences in the brain and prevents stress-induced impairment of spatial memory. *Behav Brain Res* 2009; 200: 15-21.
- 41) YASUI K, BABA A. Therapeutic potential of superoxide dismutase (SOD) for resolution of inflammation. *Inflamm Res* 2006; 55: 359-363.
- 42) BERTOLOTTO F, MASSONE A. Combination of alpha lipoic acid and superoxide dismutase leads to physiological and symptomatic improvements in diabetic neuropathy. *Drugs R D* 2012; 12: 29-34.
- 43) LETIZIA MAURO G, CATALDO P, BARBERA G, SANFILIPPO A. α -Lipoic acid and superoxide dismutase in the management of chronic neck pain: a prospective randomized study. *Drugs R D* 2014; 14: 1-7.
- 44) BATTISTI E, ALBANESE A, GUERRA L, ARGNANI L, GIORDANO N. Alpha lipoic acid and superoxide dismutase in the treatment of chronic low back pain. *Eur J Phys Rehabil Med* 2013; 49: 1-6.
- 45) KHADILKAR A, ODEBIYI DO, BROUSSEAU L, WELLS GA. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Syst Rev* 2008; (4): CD003008.
- 46) DI CIACCIO E, POLASTRI M, BIANCHINI E, GASBARRINI A. Herniated lumbar disc treated with Global Postural Reeducation. A middle-term evaluation. *Eur Rev Med Pharmacol Sci* 2012; 16: 1072-1077.